Original Article

Evaluation of the Effect of N-acetylcysteine in the Prevention of Colistin Nephrotoxicity in Critically Ill Patients: A Randomized Controlled Trial

Amir Mohammad Shabani[1], Ahmad Alikhani[2], Fatemeh Heydari[3], Abolfazl Hosseinnataj[4], Masoomeh Sohrabi[1], Sima Ramezaninejad[1], Shahram Ala[1], Hamideh Abbaspour Kasgari[5]

[1]Department of Clinical Pharmacy, School of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran

[2]Department of Infectious Diseases, School of Medicine, Antimicrobial Resistance Research Center, Communicable Diseases Institute, Ghaem Shahr Razi Hospital, Mazandaran University of Medical Sciences, Sari, Iran

[3]Department of Anesthesiology, School of Medicine, Sari Imam Khomeini Hospital, Mazandaran University of Medical Sciences, Sari, Iran

[4]Department of Biostatistics and Epidemiology, School of Health, Mazandaran University of Medical Sciences, Sari, Iran

[5]Department of Clinical Pharmacy, School of Pharmacy, Antimicrobial Resistance Research Center, Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran

Received: 22-06-2024.
Revised: 11-08-2024.
Accepted: 13-09-2024.
Published: 11-03-2025.

ABSTRACT

Objective: The present study aimed to evaluate the efficacy of N-acetylcysteine (NAC) in preventing nephrotoxicity in critically ill patients receiving colistin. **Methods:** In a randomized, controlled clinical trial, eligible participants receiving colistin were divided into two groups: the drug group (n = 24) and the control group (n = 24). In the drug group, 2 g of NAC was administered intravenously daily for 5 days, simultaneously with colistin. The patients in the control group received only colistin. Serum creatinine (SCr), blood urea nitrogen (BUN), and creatinine clearance (CrCl) at baseline and on each day, and the number of cases of acute kidney injury during the study were recorded. Urinary N-acetyl-beta-D-glucosaminidase (NAG) was determined before the start of treatment and on day 5. The study outcomes were the mortality rate, length of intensive care unit (ICU) stay, and NAG levels. Finally, the values were compared between the groups. **Findings:** It was found that the 28-day mortality rate (P = 0.540) and length of ICU stay (P = 0.699) were not significantly improved by coadministration of intravenous N-acetylcysteine with colistin. SCr and BUN showed no significant reduction, and there were no changes in CrCl at the end of treatment. The changes in urinary NAG levels did not differ significantly between the two groups. There was also no difference in the stages of the RIFLE criteria (P = 0.641), and most patients were in the normal stage (58.3%). **Conclusion:** Concomitant administration of intravenous NAC at a dose of 2 g daily does not prevent colistin-induced nephrotoxicity, 28-day mortality, and length of ICU stay in critically ill patients.

Keywords: *Colistin, critically ill, N-acetyl-beta-D-glucosaminidase, N-acetylcysteine, nephrotoxicity*

Introduction

Colistin (polymyxin E) belongs to the polymyxin family. It is a cationic polypeptide antibiotic used

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jrpp

DOI: 10.4103/jrpp.jrpp_55_24

Address for correspondence:
Dr. Hamideh Abbaspour Kasgari,
E-mail: dr.abbaspour1@yahoo.com

How to cite this article: Shabani AM, Alikhani A, Heydari F, Hosseinnataj A, Sohrabi M, Ramezaninejad S, *et al.* Evaluation of the effect of N-acetylcysteine in the prevention of colistin nephrotoxicity in critically ill patients: A randomized controlled trial. J Res Pharm Pract 2024;13:85-91.

as a last resort for the treatment of multidrug-resistant Gram-negative bacteria, including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterobacteriaceae,* and *Acinetobacter Baumannii*.[1] Pharmacokinetic and pharmacodynamic studies suggest that the currently prescribed dose of colistin does not achieve adequate plasma concentrations in critically ill patients. A higher dose is required to prevent resistance and achieve the desired bactericidal effect.[2] The incidence of nephrotoxicity of colistin is approximately 20% to 60%[3] and is influenced by many risk factors, including dosage and patient-related characteristics such as age, preexisting renal disease, diabetes, hypoalbuminemia, and concomitant use of other nephrotoxic agents.[4]

Colistin nephrotoxicity usually occurs within the first 5 days of treatment and can lead to acute kidney injury (AKI). Although nephrotoxicity is reversible by discontinuation of colistin, colistin dose limitation is the most important complication.[5] However, nephrotoxicity rarely results in permanent damage, with the percentage of cases requiring renal replacement therapy and dialysis being approximately 1.1% and 2.16%, respectively.[4] The mechanism of colistin-induced nephrotoxicity is not fully understood. Recent studies suggest that oxidative stress plays a significant role in triggering this adverse effect.[6-8] Antioxidants such as melatonin,[9] Vitamins E and C,[10] lycopene,[11] and astaxanthin[12] may alleviate kidney damage.

N-acetylcysteine (NAC) is a precursor in the formation of glutathione in the body. It has an antioxidant effect and scavenges free radicals.[13] NAC can exert its antioxidant effect directly and react with the electrophilic groups of free radicals through its thiol group.[14] Studies have shown that NAC attenuates the nephrotoxic effects of vancomycin,[15] cisplatin,[16] and gentamicin.[17] An animal study also showed that the simultaneous administration of NAC with colistin reduces the oxidative stress caused by colistin in the kidney cells.[18] However, there is only one study conducted with effervescent tablets of NAC, 1200 mg per day, in Iran in different hospital departments,[19] not in critically ill patients.

Therefore, the present study aimed to clinically evaluate the potential efficacy of intravenous and higher-dose NAC in preventing this complication in critically ill patients within the intensive care unit (ICU).

N-acetyl-beta-D-glucosaminidase (NAG), a novel biomarker for AKI, is a lysosomal enzyme localized in the proximal tubule.[10] The increase in NAG was reported in diabetic nephropathy, chronic glomerular disease, delayed renal allograft function, and nephrotoxic drug exposure. It was also more sensitive for the diagnosis of AKI in critically ill patients and preceded increased serum creatinine (SCr) by 12 h to 4 days. One study showed that higher urinary NAG levels in patients with AKI were associated with a higher likelihood of hemodialysis and an increased risk of mortality.[11,20]

Methods

In this randomized controlled clinical trial, we analyzed the data of patients who received colistin against MDR pathogens from October 2023 to March 2024 in the ICUs of Imam Khomeini Hospital in Iran, which is affiliated with Mazandaran University of Medical Sciences (MAZUMS). The research protocol was registered in the Iranian Registry of Clinical Trials (IRCT) with the code IRCT IRCT20200328046886N5.

The inclusion criteria were: (1) age 18 years and above, (2) received colistin for at least 5 days. Exclusion criteria were (1) patients who received NAC 24 h before the first colistin dose; (2) renal replacement therapy or abnormal renal function tests before the start of colistin treatment; (3) patients who received iodinated contrast media; (4) pregnant or lactating women; (5) history of cardiopulmonary resuscitation; (6) systolic blood pressure <90 mmHg; (7) patients receiving vasopressors; and (8) estimated glomerular filtration rate (eGFR) <60 mL per minute per 1.73 m^2.

Written informed consent was obtained from all participants or their relatives. The MAZUMS Research Ethics Committee approved the research protocol with the ethical code IR.MAZUMS.REC.1402.1783.

Subjects who, for any reason, were taking colistin at the dose adjusted to their eGFR in two divided doses and met other inclusion criteria were divided into the intervention and a control group. The block randomization method was used for randomization. For this purpose, four blocks were used, and patients were divided into two groups based on the sequences established in the randomized blocks. The principal and corresponding author of the study (H. Abbaspour Kasgari) designed the random allocation sequence; F. Heydari and A. M. Shabani recruited the participants and F. Heydari allocated the participants to the interventions. The demographic and clinical characteristics of the patients were recorded, including age, gender, comorbidities, and Acute Physiology and Chronic Health Evaluation II score. Intravenous NAC at a dose of 2 g was prescribed to patients in the drug group simultaneously with colistin for at least 5 days as a 24-h infusion together with a daily fluid intake, whereas patients in the control group received only colistin. Patients were excluded from the study if colistin was discontinued for reasons other than AKI. In the case of AKI, a decision was made based on

the medical team's decision on whether to terminate or continue treatment with colistin.

The blood tests performed on the day colistin treatment was started (SCr, blood urea nitrogen [BUN], albumin, hemoglobin, white blood cell), and renal function test (SCr and BUN) were measured daily. Antibiotics used with colistin, 28-day mortality, and length of ICU stay were also recorded. The primary endpoint was 28-day mortality. Secondary endpoints were the length of ICU stay and changes in urinary NAG levels.

Creatinine clearance (CrCl) was calculated according to the Cockcroft–Gault equation.[21] Urinary NAG levels were measured in all patients before administration of a colistin dose (day 0) and on the 5th day of treatment and recorded as an index of AKI. The following values, according to RIFLE criteria, were used to determine AKI: risk (increasing SCr × 1.5 or decreasing GFR >25%), injury (increasing SCr × 2 or decreasing GFR >50%), failure (increasing SCr × 3 or decreasing GFR >75%), loss of renal function (complete loss of renal function >4 weeks), and end-stage renal disease (ESRD) (complete loss of renal function >3 months).[22]

To determine urinary NAG levels, fresh urine samples were collected from the patients and stored in the freezer at − 20°C. At the end of the study, all samples were removed from the freezer and centrifuged at room temperature for 15 min after thawing. The concentration of NAG in urine was measured using an enzyme-linked immunosorbent assay kit (ZellBio GmbH, Germany) according to the manufacturer's instructions (Cat. No.: ZB-10828C-H9648).

The sample size was calculated based on findings from an animal study by Ceylan *et al*.[7] In this study, the number of samples in each colistin and colistin plus NAC group was eleven (22 in total). Considering that the number of samples can be increased by a multiple of 2 or 3 to extrapolate the findings from the animal study to the human study, taking into account the multiple of 2 results in a number of 44 subjects in this study. Finally, if the 10% dropouts are included, the number increases to 48 persons (24 persons in each group). SPSS software version 24 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis, and $P < 0.05$ was considered statistically significant.

Results

During the study period, 310 patients were admitted to the ICUs. Of these, 50 patients met the inclusion criteria and were included in the study. Two patients died during the follow-up period. A total of 24 patients in the drug group and 24 patients in the control group completed the study [Figure 1].

Table 1 presents the demographic and clinical data for the patients in both groups, revealing no significant differences concerning these parameters. Similarly, no differences were observed in the concentrations of leukocytes, hemoglobin, and albumin.

Meropenem (58.3%) and vancomycin (50%) were the most commonly coadministered antibiotics. Meropenem, linezolid, and nebulized colistin were prescribed more

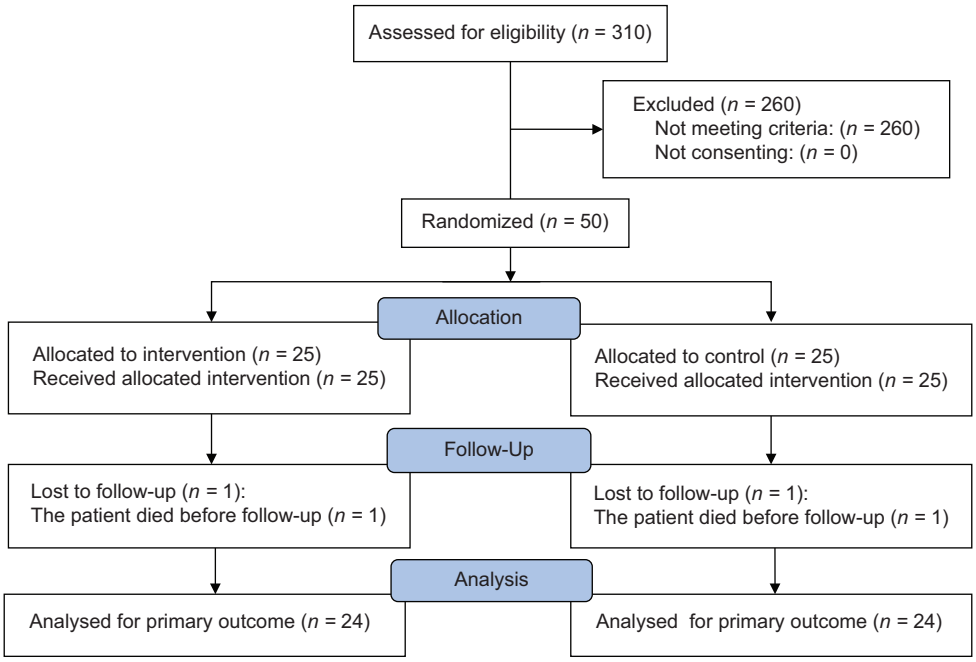

Figure 1: CONSORT flow diagram

Table 1: Demographic and clinical data of the patients

Parameter	Total (*n*=48)	NAC group (*n*=24)	Control group (*n*=24)	*P*
Gender				
Female	18 (37.5)	6 (25.0)	12 (50.0)	0.074⁺
Male	30 (62.5)	18 (75.0)	12 (50.0)	
Age	48.92±19.63	47.25±22.46	50.58±16.65	0.562*
APACHE II	14.06±5.19	14.42±4.52	13.71±5.85	0.641*
WBC (×10³ cells/µL)		13.74±6.31	11.87±6.41	0.314*
Hemoglobin (g/dL)		9.84±1.33	10.15±2.41	0.587*
Albumin (g/dL)		3.06±0.52	3.09±0.54	0.828*
Past medical history	22 (45.8)	9 (37.5)	13 (54.2)	0.247⁺
HTN	9 (40.9)	4 (44.4)	5 (38.5)	0.779⁺
DM	9 (40.9)	5 (55.6)	4 (30.8)	0.245⁺
IHD	4 (18.2)	2 (22.2)	2 (15.4)	0.999⁺
Malignancy	2 (9.1)	0	2 (15.4)	0.494⁺
DLP	3 (13.6)	1 (11.1)	2 (15.4)	0.999⁺
Psychiatric disorder	2 (9.1)	0	2 (15.4)	0.494⁺
Hypothyroidism	5 (22.7)	2 (22.2)	3 (23.1)	0.999⁺
Epilepsy	3 (13.6)	2 (22.2)	1 (7.7)	0.544⁺
Parkinson	3 (13.6)	0	3 (23.1)	0.240⁺
Alzheimer	1 (4.5)	0	1 (7.7)	0.999⁺
CVA	3 (13.6)	1 (11.1)	2 (15.4)	0.999⁺
Tuberculosis	1 (4.5)	0	1 (7.7)	0.999⁺
COPD	3 (13.6)	1 (11.1)	2 (15.4)	0.999⁺
Asthma	1 (4.5)	0	1 (7.7)	0.999⁺

*Independent samples *t*-test, ⁺Chi-square test. Data is presented as mean±SD or *n* (%) where applicable. SD=Standard deviation, WBC=White blood cell, HTN=Hypertension, DM=Diabetes mellitus, IHD=Ischemic heart disease, DLP=Dyslipidemia, CVA=Cerebrovascular accident, COPD=Chronic obstructive pulmonary disorder, NAC=Nacetylcysteine, APACHE II=Acute physiology and chronic health evaluation

frequently in the NAC group than in the control group. There were no differences between the two groups for other antibiotics and drugs that could have toxic effects on renal function.

Stenotrophomas maltophilia and *Serratia* were the most frequently detectable microorganisms in the culture results. Table 2 shows the SCr, BUN, and CrCl changes in patients in the NAC and control groups. There was no significant difference in the three parameters between the two groups. The two groups also differed in the Cr and CrCl parameters regarding the trend of changes, i.e. an increase or decrease in Cr and Cr–Cl in the control group.

Table 3 shows the incidence of AKI according to the RIFLE criteria, including stages, in both groups. As can be seen, most patients were in the normal stage (58.3%), and four patients (8.3%) experienced failure, with only 1 out of 4 in the NAC group. Only one patient (2.1%) from the control group suffered ESRD. However, the differences between the two groups were not statistically significant. The two groups had no difference in the 28-day mortality rate. The length of stay in the ICU was one of the secondary endpoints for which there was no significant difference between the two groups.

Changes in NAG urine levels, the other secondary endpoint, did not differ significantly between the two groups, as shown in Table 4.

Discussion

Our study found that the 28-day mortality rate, ICU length of stay, and urinary NAG levels were not significantly improved by the coadministration of intravenous N-acetylcysteine with colistin. In addition, SCr and BUN were not significantly reduced, CrCl levels did not change at the end of treatment, and NAC did not prevent the occurrence of AKI in patients receiving colistin. Most studies on the reduction of colistin-induced nephrotoxicity have been conducted in animal models.[7,18] Some studies investigated antioxidants and other pharmacologic agents to prevent colistin nephrotoxicity. The concomitant use of antioxidants (melatonin, Vitamins C and E, silymarin and curcumin, NAC, etc.) may have a protective effect during colistin exposure.[23]

In a retrospective cohort study, Bozkurt *et al*. investigated the association between NAC intake and colistin-related nephrotoxicity. They found that NAC intake did not contribute to the prevention of

Table 2: Comparison of kidney function between two groups

Parameter	Day	NAC group (*n*=24)	Control group (*n*=24)	*P**
SCr (mg/dL)	0	0.75±0.24	1.14±1.70	0.685
	1	0.75±0.26	0.95±0.54	0.406
	2	0.73±0.25	1.06±0.72	0.139
	3	0.75±0.30	1.16±0.93	0.371
	4	0.80±0.34	1.27±0.89	0.072
	5	0.90±0.54	1.42±0.97	0.066
	P⁺	0.265	<0.001	
BUN (mg/dL)	0	20.71±10.74	26.63±19.61	0.358
	1	21.83±11.85	27.13±19.22	0.489
	2	21.92±12.73	27.63±22.45	0.695
	3	22.92±14.88	30.71±28.54	0.901
	4	22.75±15.36	33.58±26.64	0.265
	5	24.25±16.64	35.58±26.64	0.177
	P⁺	0.973	0.136	
CrCl (mL/min)	0	145.88±71.86	130.46±73.42	0.483
	5	140.25±75.93	100.17±75.50	0.051
	*P*ˣ	0.275	<0.001	

*Mann–Whitney test, ⁺Freidman test, ˣWilcoxon test. Data is presented as mean±SD. SCr=Serum creatinine level, BUN=Blood urea nitrogen, CrCl=Creatinine clearance, NAC=Nacetylcysteine

Table 3: Comparison of the acute kidney injury stages between two groups

Parameter	Total (*n*=48)	NAC group (*n*=24)	Control group (*n*=24)	*P**
RIFLE criteria				
Normal	28 (58.3)	16 (66.7)	12 (50.0)	0.641
Risk	10 (20.8)	5 (20.8)	5 (20.8)	
Injury	5 (10.4)	2 (8.3)	3 (12.5)	
Failure	4 (8.3)	1 (4.2)	3 (12.5)	
Loss	0	0	0	
ESRD	1 (2.1)	0	1 (4.2)	

*Chi-square test. Data is presented as *n* (%). ESRD=End-stage renal disease, NAC=Nacetylcysteine

Table 4: Change of urinary N-acetyl-beta-D-glucosaminidase level in two groups

Day	NAC group	Control group	Difference	*P**
0	18.09±2.97	18.56±4.40	−0.46±5.91	0.706
5	17.87±3.01	18.87±3.71	−0.99±4.36	0.373
Difference	0.23±2.98	−0.30±3.87	0.53±5.15	0.681
P⁺	0.744	0.533	-	-

*Independent samples *t*-test, ⁺Paired samples *t*-test. NAC=Nacetylcysteine

colistin-induced nephrotoxicity, and the incidence of AKI was similar in both groups. These results are consistent with our study.[24] Shariatmaghani *et al*. investigated the incidence of colistin-associated nephrotoxicity and the role of other confounding factors in the incidence of AKI in critically ill patients. Although this prospective cohort study did not specifically examine the effect of NAC, the incidence of AKI was higher in the NAC group than in the control group with younger age.[25] Timuroğlu *et al*. retrospectively studied AKI in patients who had received colistin with NAC in mucolytic doses in the ICU. There was no significant difference between the AKI rate, mortality rate, number of days of mechanical ventilation, and length of stay in the ICU between the NAC and non-NAC groups. There was no association between the eGFR value during hospitalization and the development of AKI after using colistin.[26] It was similar to our study. Mosayebi *et al*. investigated the efficacy of NAC in colistin nephrotoxicity in a randomized controlled clinical trial. They found that concomitant administration of NAC at a dose of 1200 mg daily had no effect in preventing colistin-induced nephrotoxicity.[19]

Our study population was critically ill patients without septic shock. The incidence of colistin-induced AKI has been reported to be approximately 12.7%–70% in ICU studies.[6,12,13,27] A higher incidence of AKI is reported in the kidney disease: Improving Global Outcomes criteria due to the lower threshold of AKI definitions, as an increase in creatinine of 1.5 from baseline is considered AKI Stage 1, whereas in the RIFLE definition, this is considered AKI risk.[4]

Most of our patients were in the fluid resuscitation phase, and their initial CrCl was high. This could be due to augmented renal clearance, defined as a CrCl >130 mL/min, present in 20%–65% of critically ill patients. Younger age, multiple trauma, and lower severity of illness have been identified as risk factors.[28] These characteristic features are consistent with those of our patients.

Our analysis has several strengths. Vasopressor use in critically ill patients was independently associated with the development of AKI during colistin treatment,[27] and our study excluded the use of vasoactive agents. This is the only clinical trial with higher doses of intravenous NAC in critically ill patients. We have used urinary NAG levels as a new biomarker for AKI in our patients. Urinary NAG has also been found to independently predict mortality or the need for dialysis in AKI patients.[5,17] Therefore, urinary NAG seems to perform best for risk prediction after AKI.[18,29]

This study has some limitations. It was an open-label study. The sample size was small, the results cannot be generalized, and the duration of the intervention was short. Nevertheless, this is the first clinical trial of high-dose intravenous NAC to prevent colistin

nephrotoxicity and to measure NAG as a biomarker for AKI. Further randomized, placebo-controlled trials, longer intervention duration, and a larger sample size are needed to achieve better results.

Authors' Contribution

A. Alikhani and H. Abbaspour Kasgari conceived the study and revised the manuscript. Fatemeh Heydari prescribed the medication and helped with the administration and care of the patients. A. Hosseinnattaj worked on the statistical analysis. S. Ala was the study advisor. A. M. Shabani, M. Sohrabi and S. Ramezaninejad collected the data of the patients and monitored them during the study intervention and follow-up of the patients. A. M. Shabani performed the tests on the urine samples and drafted the main manuscript.

Acknowledgments

The authors would like to express their gratitude to the staff of the Intensive Care Unit at Imam Khomeini Hospital for their kind support. Vice-Chancellery for Research and Technology of MAZUMS.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Grégoire N, Aranzana-Climent V, Magréault S, Marchand S, Couet W. Clinical pharmacokinetics and pharmacodynamics of colistin. Clin Pharmacokinet 2017;56:1441-60.
2. Jacobs M, Grégoire N, Mégarbane B, Gobin P, Balayn D, Marchand S, *et al.* Population pharmacokinetics of colistin methanesulfonate and colistin in critically Ill patients with acute renal failure requiring intermittent hemodialysis. Antimicrob Agents Chemother 2016;60:1788-93.
3. Chien HT, Lin YC, Sheu CC, Hsieh KP, Chang JS. Is colistin-associated acute kidney injury clinically important in adults? A systematic review and meta-analysis. Int J Antimicrob Agents 2020;55:105889.
4. Rabi R, Enaya A, Sweileh MW, Aiesh BM, Namrouti A, Hamdan ZI, *et al.* Comprehensive assessment of colistin induced nephrotoxicity: Incidence, risk factors and time course. Infect Drug Resist 2023;16:3007-17.
5. Sirijatuphat R, Limmahakhun S, Sirivatanauksorn V, Nation RL, Li J, Thamlikitkul V. Preliminary clinical study of the effect of ascorbic acid on colistin-associated nephrotoxicity. Antimicrob Agents Chemother 2015;59:3224-32.
6. Lee TW, Bae E, Kim JH, Jang HN, Cho HS, Chang SH, *et al.* The aqueous extract of aged black garlic ameliorates colistin-induced acute kidney injury in rats. Ren Fail 2019;41:24-33.
7. Ceylan B, Ozansoy M, Kılıç Ü, Yozgat Y, Ercan Ç, Yıldız P, *et al.* N-acetylcysteine suppresses colistimethate sodium-induced nephrotoxicity via activation of SOD2, eNOS, and MMP3 protein expressions. Ren Fail 2018;40:423-34.
8. Dai C, Tang S, Velkov T, Xiao X. Colistin-induced apoptosis of neuroblastoma-2a cells involves the generation of reactive oxygen species, mitochondrial dysfunction, and autophagy. Mol Neurobiol 2016;53:4685-700.
9. Yousef JM, Chen G, Hill PA, Nation RL, Li J. Melatonin attenuates colistin-induced nephrotoxicity in rats. Antimicrob Agents Chemother 2011;55:4044-9.
10. Ghlissi Z, Hakim A, Mnif H, Zeghal K, Rebai T, Boudawara T, *et al.* Combined use of Vitamins E and C improve nephrotoxicity induced by colistin in rats. Saudi J Kidney Dis Transpl 2018;29:545-53.
11. Dai C, Tang S, Deng S, Zhang S, Zhou Y, Velkov T, *et al.* Lycopene attenuates colistin-induced nephrotoxicity in mice via activation of the Nrf2/HO-1 pathway. Antimicrob Agents Chemother 2015;59:579-85.
12. Ghlissi Z, Hakim A, Sila A, Mnif H, Zeghal K, Rebai T, *et al.* Evaluation of efficacy of natural astaxanthin and Vitamin E in prevention of colistin-induced nephrotoxicity in the rat model. Environ Toxicol Pharmacol 2014;37:960-6.
13. Hara Y, McKeehan N, Dacks PA, Fillit HM. Evaluation of the neuroprotective potential of N-acetylcysteine for prevention and treatment of cognitive aging and dementia. J Prev Alzheimers Dis 2017;4:201-6.
14. Pei Y, Liu H, Yang Y, Yang Y, Jiao Y, Tay FR, *et al.* Biological activities and potential oral applications of N-acetylcysteine: Progress and prospects. Oxid Med Cell Longev 2018;2018:2835787.
15. Badri S, Soltani R, Sayadi M, Khorvash F, Meidani M, Taheri S. Effect of N-acetylcysteine against vancomycin-induced nephrotoxicity: A randomized controlled clinical trial. Arch Iran Med 2020;23:397-402.
16. Sancho-Martínez SM, Prieto-García L, Prieto M, Fuentes-Calvo I, López-Novoa JM, Morales AI, *et al.* N-acetylcysteine transforms necrosis into apoptosis and affords tailored protection from cisplatin cytotoxicity. Toxicol Appl Pharmacol 2018;349:83-93.
17. Borisenok OA, Bushma MI, Baraban OV, Zimatkin SM. Therapeutic effect of acetylcysteine on rats with gentamicin-induced nephropathy. Eksp Klin Farmakol 2012;75:10-3.
18. Ozyilmaz E, Ebinc FA, Derici U, Gulbahar O, Goktas G, Elmas C, *et al.* Could nephrotoxicity due to colistin be ameliorated with the use of N-acetylcysteine? Intensive Care Med 2011;37:141-6.
19. Mosayebi S, Soltani R, Shafiee F, Assarzadeh S, Hakamifard A. Evaluation of the effectiveness of N-acetylcysteine in the prevention of colistin-induced nephrotoxicity: A randomized controlled clinical trial. J Res Pharm Pract 2021;10:159-65.
20. Fan H, Zhao Y, Sun M, Zhu JH. Urinary neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, N-acetyl-β-D-glucosaminidase levels and mortality risk in septic patients with acute kidney injury. Arch Med Sci 2018;14:1381-6.
21. Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. Clin J Am Soc Nephrol 2010;5:1003-9.
22. Lin CY, Chen YC. Acute kidney injury classification: AKIN and RIFLE criteria in critical patients. World J Crit Care Med 2012;1:40-5.
23. Jafari F, Elyasi S. Prevention of colistin induced nephrotoxicity: A review of preclinical and clinical data. Expert Rev Clin Pharmacol 2021;14:1113-31.
24. Bozkurt I, Sharma A, Esen S. Colistin-induced nephrotoxicity and the role of N-acetylcysteine: A retrospective cohort study. J Infect Dev Ctries 2017;11:895-9.
25. Shariatmaghani S, Shariatmaghani SS, Sedaghat A, Najafi M,

Moghaddam A. Colistin-associated acute kidney injury in intensive care unit patients: Significance of other confounding factors. Int Res J Med Med Sci 2019;7:91-8.
26. Timuroğlu A, Muslu S, Menteş S, Ünver S. Effect of N-acetyl cysteine on acute kidney injury in patients with colistin used in intensive care; retrospective study. Acta Oncol Turc 2018;51:390-8.
27. Kilic I, Ayar Y, Ceylan İ, Kaya PK, Caliskan G. Nephrotoxicity caused by colistin use in ICU: A single Centre experience. BMC Nephrol 2023;24:302.
28. Bilbao-Meseguer I, Rodríguez-Gascón A, Barrasa H, Isla A, Solinís MÁ. Augmented renal clearance in critically Ill patients: A systematic review. Clin Pharmacokinet 2018;57:1107-21.
29. Mohkam M, Ghafari A. The role of urinary N-acetyl-beta-glucosaminidase in diagnosis of kidney diseases. J Pediatr Nephrol 2015;3:84-91.